Attorney Docket No. 26230

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

DIETRICH, et al.

Serial No.: 10/505,138 Art Unit: 1615

Filed: August 19, 2004 Examiner: SILVERMAN, E.

For: **ORAL DOSAGE FORM CONTAINING A PDE4 INHIBITOR AS AN ACTIVE INGREDIENT AND POLYVINYLPYRROLIDON AS EXCIPIENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Declaration Under 37 CFR 1.132

1. I, Hartmut NEY, declare and say:

1.1. That I am a citizen of the Federal Republic of Germany, residing at Peter-Thumb-Str. 46, Konstanz 78464.

1.2. That I have expert knowledge of the subject matter of the captioned application for U.S. Letters Patent.

1.3. That, I have studied Pharmacy at the University of Mainz, Germany.

1.4. That, I am currently working as Development Scientist at Pharmaceutical Development of ALTANA Pharma AG.

2. Summary and Traversal of the 35 U.S.C. §103 rejections

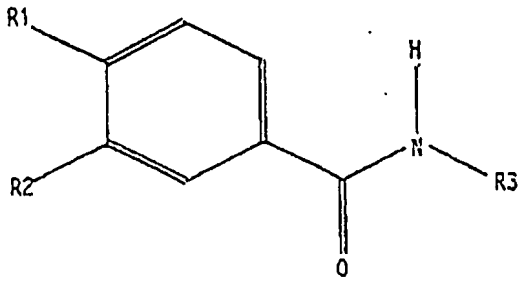
2.1 I have intensively studied the Office Action dated November 3, 2006, as well as the cited prior art:

a) US 2003/0018071 to Rennard et al.;

b) US 6,677,362 to Ghebre-Sellassie et al.; and

c) US 4,024,240 to Thakkar.

2.2 Claim 18 of the present invention in the actual wording relates to "[a] solid dosage form in tablet or pellet form for oral administration of a PDE 4 inhibitor, comprising a PDE 4 inhibitor together with polyvinylpyrrolidone as binder, and one or more other suitable pharmaceutical excipients, wherein the PDE 4 inhibitor is a compound of the formula I



(I)

in which

R1 is difluoromethoxy,

R2 is cyclopropylmethoxy and

R3 is 3,5-dichloropyrid-4-yl,

or a salt of this compound, an N-oxide of the pyridine of this compound or a salt thereof, wherein said dosage form

has immediate release of the PDE 4 inhibitor, and wherein the polyvinylpyrrolidone is selected from the group consisting of polyvinylpyrrolidone of molecular weight 28,000 - 34,000, polyvinylpyrrolidone of molecular weight 44,000 - 54,000 and polyvinylpyrrolidone of molecular weight 1,000,000 - 1,500,000.

2.3 The primary Rennard et al. reference teaches the combination of certain PDE4 inhibitors with a pharmaceutical carrier. The Rennard et al. reference does not teach each and every element of the presently pending claims. In particular, it neither teaches compositions containing PVP in any amount, nor specific molecular weight ranges for the PVP as presently claimed. Further, the Rennard et al. reference does not discuss the solubility of drugs. Further, Rennard et al. do not recognize the need for an immediate release dosage form containing polyvinylpyrrolidone (PVP) because they already teach an "immediate release" tablet in Example 4 at Table 2 which does not contain PVP. Accordingly, the cited art does not provide motivation to obtain an "immediate release" tablet by combining the embodied disclosure with any other reference, since Rennard already teaches an "immediate release" tablet.

2.4. The secondary Ghebre-Sellassie, et al. reference merely states that compositions comprising a carrier polymer such as PVP, "increase the bioavailability of various water insoluble

drugs by increasing their dissolution rates…" (See col. 2, line 67 - col. 3, line 1). No degree of dissolution increase is provided in the cited art of record. No comparative data is provided in the cited art of record. As such, the cited art of record is simply an invitation to experiment to determine which types of PVP are useful to provide an acceptable dissolution profile.

2.5. In addition, Ghebre-Sellassie requires the addition of a unique third component, a plasticizer/solubilizer, in addition to the antibiotic and PVP, in order to attain an increased dissolution rate. See col. 3, line 64, to col. 4, line 8, and claim 1 at col. 6, lines 2-6. As such, Ghebre-Sellassie appears to suggest that the form of PVP is not critical, but its combination with a required plasticizer/solubilizer is the critical element. Accordingly, the cited art of record is also simply an invitation to experiment to determine which types of plasticizers/solubilizers in combination with PVP are useful to provide an acceptable dissolution profile.

2.6. The Thakkar reference teaches antibiotic compositions which contain PVP having a molecular weight in a broad range of 10,000 - 360,000. Thakkar discloses at col. 4, lines 54-58 that "although the molecular weight of the PVP is <u>not a critical feature</u> of the dispersions of this invention,

especially-preferred dispersions are those prepared with a PVP having a molecular weight in the range of about 10,000 to about 60,000." (emphasis added) Thus, the Thakkar reference does not recognize the importance that the molecular weight of the PVP has on a dissolution profile of a particular drug.

2.7. Accordingly, the art cited by the Examiner: 1) does not disclose each and every element of the presently claimed invention; 2) Even if the cited art did independently teach each and every element of the presently pending claims, there is absolutely no motivation to combine the Rennard and Ghebre-Sellassie et al. references since Rennard did not recognize the need for an immediate release formulation containing PVP; 3) the Ghebre-Sellassie et al. reference is an invitation to experiment with different PVP molecular weights; and 4) the Thakkar reference does not recognize the impact that the molecular weight of a particular PVP has on the dissolution profile of a particular drug.

2.8. Furthermore, presented herewith, in Appendix A, is a compilation of methods and data gathered during studies in our laboratory of: 1) the solubility for physical mixtures and various solid dispersions of pure roflumilast (containing no PVP or carriers) vs. the solubility of

roflumilast in formulations containing PVP of a certain molecular weight range; and 2) the dissolution of roflumilast in a tablet formulation containing PVP of a certain molecular weight range vs. the dissolution of roflumilast in a tablet formulation containing other carriers, but no PVP. I hereby declare and state I have either conducted or supervised the work described here and in Appendix A. This data unequivocally and unexpectedly demonstrates that formulations containing certain molecular weights of PVP have a superior dissolution profile as compared to formulations which contain no PVP, or formulations which contain other carriers, but no PVP. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 18-23 and 25-67 under 35 USC §103(a).

2.9. If, however, the Examiner insists on maintaining that the presently pending claims are obvious in view of the deficient teachings of the cited references, applicant again respectfully draws the Examiner's attention to Appendix A which unexpectedly demonstrates that a formulation which contains PVP has an unexpectedly higher dissolution rate of roflumilast than a formulation which contains pure roflumilast and no PVP, or a formulation which contains roflumilast and other carriers, but no PVP.

3. The undersigned Declarant declares further that all statements made herein and in the Appendix of his own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issuing thereon.

Signed at Constance,
Federal Republic of Germany,

April 19, 2007.

Hartmut Ney

APPENDIX A

(I) Solubility trials of the solid dispersions: pure roflumilast vs. roflumilast with PVP of specific molecular weight.

The solubility and speed of solubility of the solid dispersions and physical mixtures were compared with the results obtained for the pure substance Roflumilast. Analysis was performed in a dissolution apparatus, whereby the quantity of the dissolved active substance was directly measured by photometry: a pump continually circulates the sample medium from the dissolution vessel through the cuvette of a photometer and back. Absorption is measured at specified intervals.

500 ml buffer pH 6.8 USP-NF with 1% SDS at a temperature of approximately 37°C is used as the release medium and the stirring speed is set to 50 rpm. Absorption is measured every 10 minutes over a period of 2 hours.

A suitable wavelength for the measurement is first determined with a sample solution containing approximately 10 mg Roflumilast in 1 litre of release medium and the E1% value is calculated. A spectrum is recorded over the range 200 - 700 nm.

Preparation of the analysis solution:

-10.01 g SDS is dissolved in 1 litre buffer pH 6.8 USP-NF

- 11.25 mg Roflumilast is dissolved in approximately 10 ml methanol
- with the aid of the buffer SDS solution, the active substance solution is transferred quantitatively to a 1000 ml volumetric flask and the solution is topped up to the mark with the buffer SDS solution

Results:

λmax	**Absorption**
214.0 nm	1.0863
255.0 nm	0.3466

The maximum at 255.0 is used for the analysis as this is less susceptible to interference than the maximum at shorter wavelengths.

The calculated E1% value for this maximum is 308.91.

Table I: Solubility vs. Time

Analysis No.	B. No.	Weight	10 min	20 min	110 min	120 min
7990002	LRe 8a	150.36 mg	100.6%	101.3%	104.4%	104.7%
7990003	LRe 8b	150.23 mg	95.5%	96.3%	99.9%	100.2%
7990004	LRe 8c	150.13 mg	84.2%	86.9%	90.8%	91.3%
7990005	LRe 8d	150.18 mg	96.3%	96.9%	100.6%	101.1%
7990006	LRe 8e	150.29 mg	79.8%	83.5%	88.0%	88.4%
7990007	AM50/046	7.52 mg	19.8%	28.1%	47.0%	48.5%
7990008	LRe 11a	150.20 mg	91.6%	93.1%	97.0%	97.3%
7990009	LRe 11b	150.50 mg	87.2%	88.0%	91.1%	91.5%
7990010	LRe 7a	150.11 mg	50.9%	59.0%	72.1%	73.1%
7990011	LRe 7b	150.56 mg	40.8%	51.7%	60.6%	61.2%
7990012	LRe 17b	150.54 mg	40.7%	60.2%	89.8%	90.2%
7990013	LRe 14c	150.15 mg	78.4%	83.8%	93.0%	94.3%
7990014	LRe 14a	150.41 mg	78.7%	89.1%	94.8%	95.2%
7990015	LRe 14b	150.50 mg	68.2%	83.1%	91.6%	92.1%
7990016	LRe 16a	150.34 mg	74.8%	77.8%	87.9%	88.4%
7990017	LRe 14d	150.31 mg	66.0%	78.1%	86.9%	87.4%
7990018	LRe 16b	150.12 mg	95.5%	96.2%	99.1%	99.5%
7990019	LRe 14f	150.44 mg	86.7%	88.9%	98.2%	98.9%

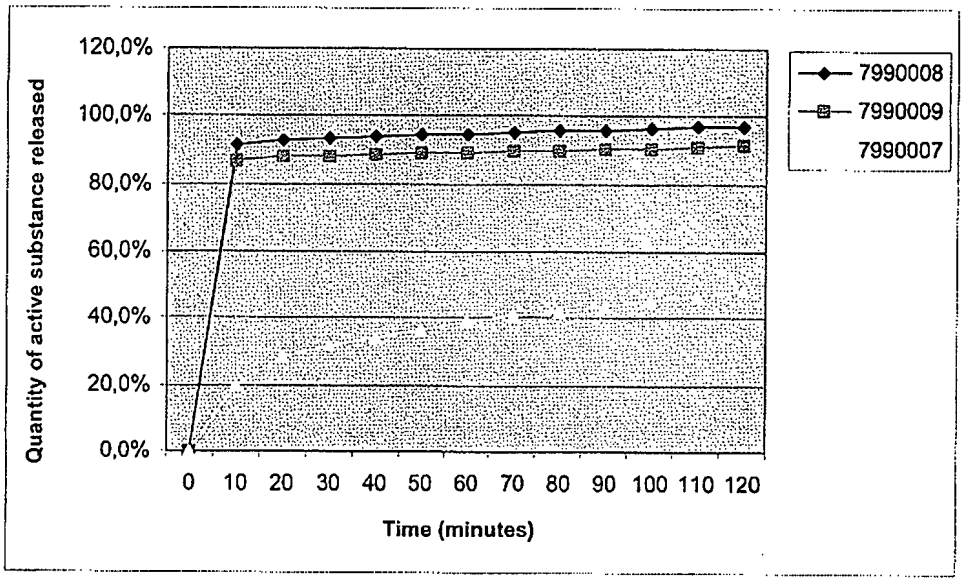
Table II: Sample Formulation and Preparation

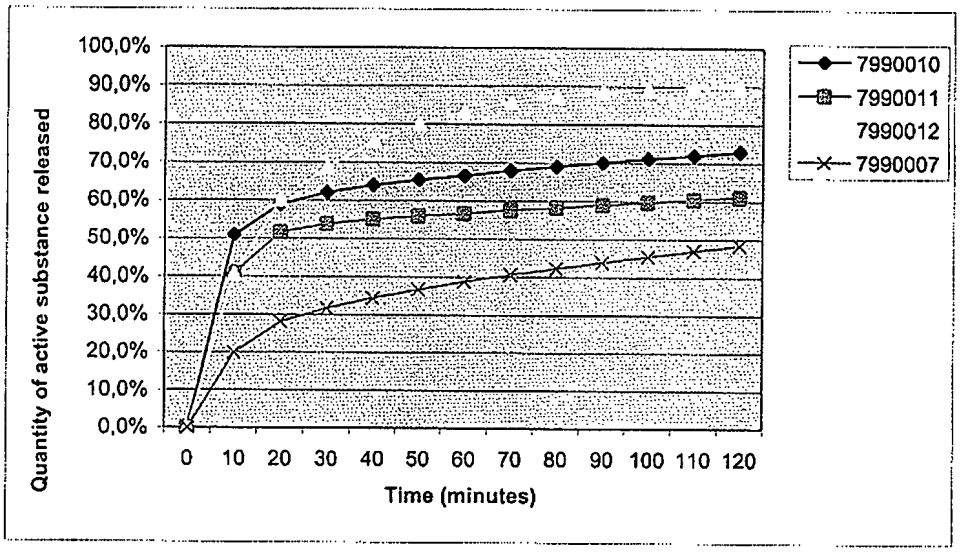
Analysis No.	B. No.	Substance	Preparation
7990002	LRe 8a	Kollidon 17PF + 5% Roflumilast	Spray drying of 5% ethanolic Kollidon solution
7990003	LRe 8b	Kollidon 17PF + 5% Roflumilast	Spray drying of 15% ethanolic Kollidon solution
7990004	LRe 8c	Kollidon 30 + 5% Roflumilast	Spray drying of 5% ethanolic Kollidon solution
7990005	LRe 8d	Kollidon 17PF + 5% Roflumilast	Spray drying of 5% Kollidon solution in isopropanol
7990006	LRe 8e	Kollidon 30 + 5% Roflumilast	Spray drying of 5% Kollidon solution in isopropanol
7990007	AM50/046	Roflumilast	
7990008	LRe 11a	Kollidon 17PF + 5% Roflumilast	Freeze drying of 15% Kollidon solution in tert. butanol
7990009	LRe 11b	Kollidon 30 + 5% Roflumilast	Freeze drying of 15% Kollidon solution in tert. butanol
7990010	LRe 7a	Kollidon 17PF + 5% Roflumilast	Physical mixture
7990011	LRe 7b	Kollidon 30 + 5% Roflumilast	Physical mixture
7990012	LRe 17b	Kollidon 90 + 5% Roflumilast	Physical mixture
7990013	LRe 14c	Kollidon 30 + 5% Roflumilast	Vacuum drying of 5% ethanolic Kollidon solution
7990014	LRe 14a	Kollidon 90 + 5% Roflumilast	Vacuum drying of 5% ethanolic Kollidon solution
7990015	LRe 14b	Kollidon 90 + 5% Roflumilast	Vacuum drying of 5% Kollidon solution in isopropanol

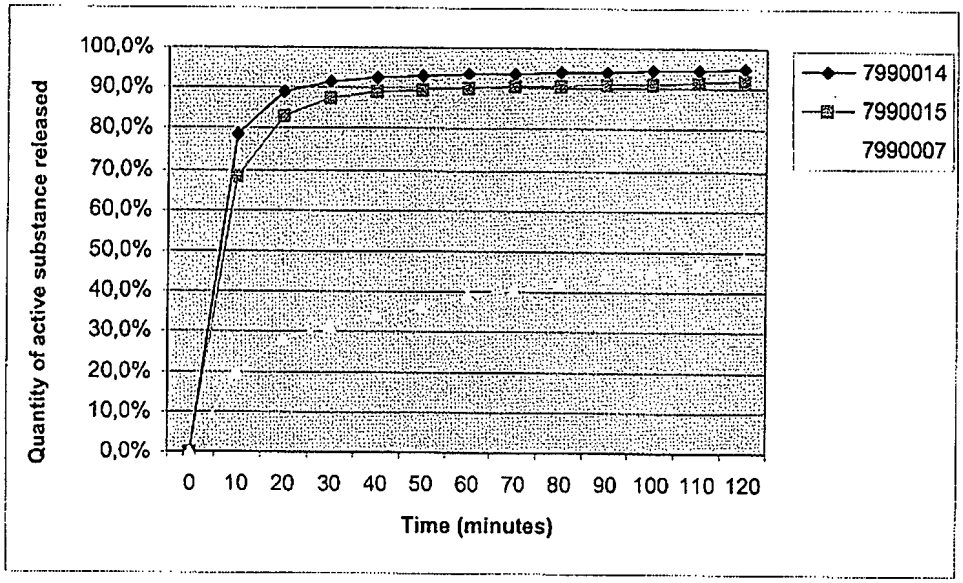
Table II: Sample Formulation and Preparation (continued)

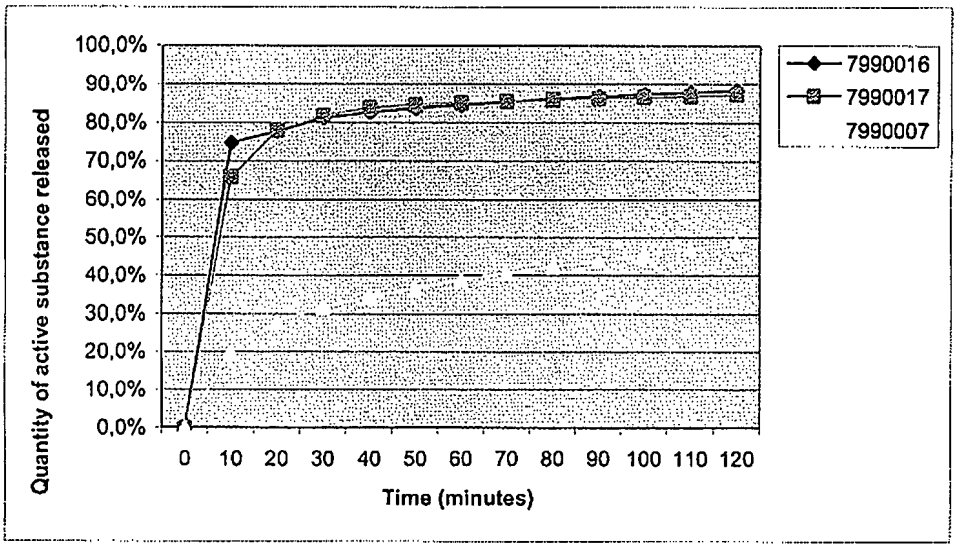
Analysis No.	B. No.	Substance	Preparation
7990016	LRe 16a	Kollidon 30 + 5% Roflumilast	Vacuum drying of 5% ethanolic Kollidon solution
7990017	LRe 14d	Kollidon 30 + 5% Roflumilast	Vacuum drying of 5% Kollidon solution in isopropanol
7990018	LRe 16b	Kollidon 17PF + 5% Roflumilast	Vacuum drying of 5% ethanolic Kollidon solution
7990019	LRe 14f	Kollidon 17PF + 5% Roflumilast	Vacuum drying of 5% Kollidon solution in isopropanol

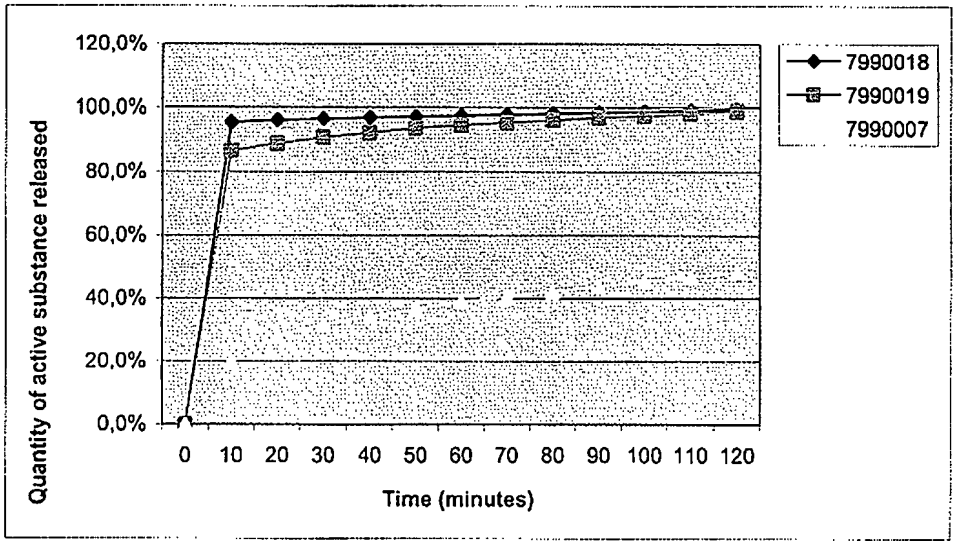
Figures 1a-1e: Solubility Data vs. Time











Results:

In comparison with substance Roflumilast alone, there was a marked improvement in solubility and speed of solubility for the physical mixtures and the various solid dispersions: the results for the solid dispersions were better than those for the physical mixtures. There were only minor differences between the solid dispersions prepared using various techniques and different Kollidons as carrier material: the results for

Kollidon 17PF were slightly better than those for Kollidon 30, while better results for solubility were obtained when ethanol rather than isopropanol was used as the solvent. On spray drying, the resultant particles are smaller in the case of the 5% solution in comparison with the 15% solution i.e. the surface area is greater and solubility is thus somewhat better. The next stage was to investigate whether this improvement in solubility could be realised in the tablet form.

(II) Tablet Formulations: comparing roflumilast with carriers, but no PVP vs. roflumilast with PVP.

There were 6 formulations of "Formula B" tested. Each "Formula B formulation" contained various amounts of roflumilast active and identical amounts of excipients. In particular, "Formula B" contained the following components in the following amounts:

a) Roflumilast: 50 µg, 125 µg, 250 µg, 500 µg, 1000 µg, and 2500 µg; b) Lactose Monohydrate: 49,660 µg in each roflumilast dosage amount;

c) Cornstarch: 13,390 µg in each roflumilast dosage amount;

d) PVP K90: 1,300 µg in each roflumilast dosage amount; and

e) Magnesium stearate: 650 µg in each roflumilast dosage amount.

Similarly, there were 6 formulations of "Formula C" tested. Each "Formula C formulation" contained various amounts of roflumilast active and identical amounts of excipients. In particular, "Formula C" contained the following components in the following amounts:

a) Roflumilast: 50 µg, 125 µg, 250 µg, 500 µg, 1000 µg, and

2500 µg; b) Lactose Monohydrate: 70,300 µg in each roflumilast dosage amount;

c) Cornstarch: 2,375 µg in each roflumilast dosage amount;

d) Potato starch: 19,475 µg in each roflumilast dosage amount;

e) Sodiumcarboxymethylstarch: 1,900 µg in each roflumilast dosage amount; and

f) Magnesium stearate: 950 µg in each roflumilast dosage amount.

50 µg

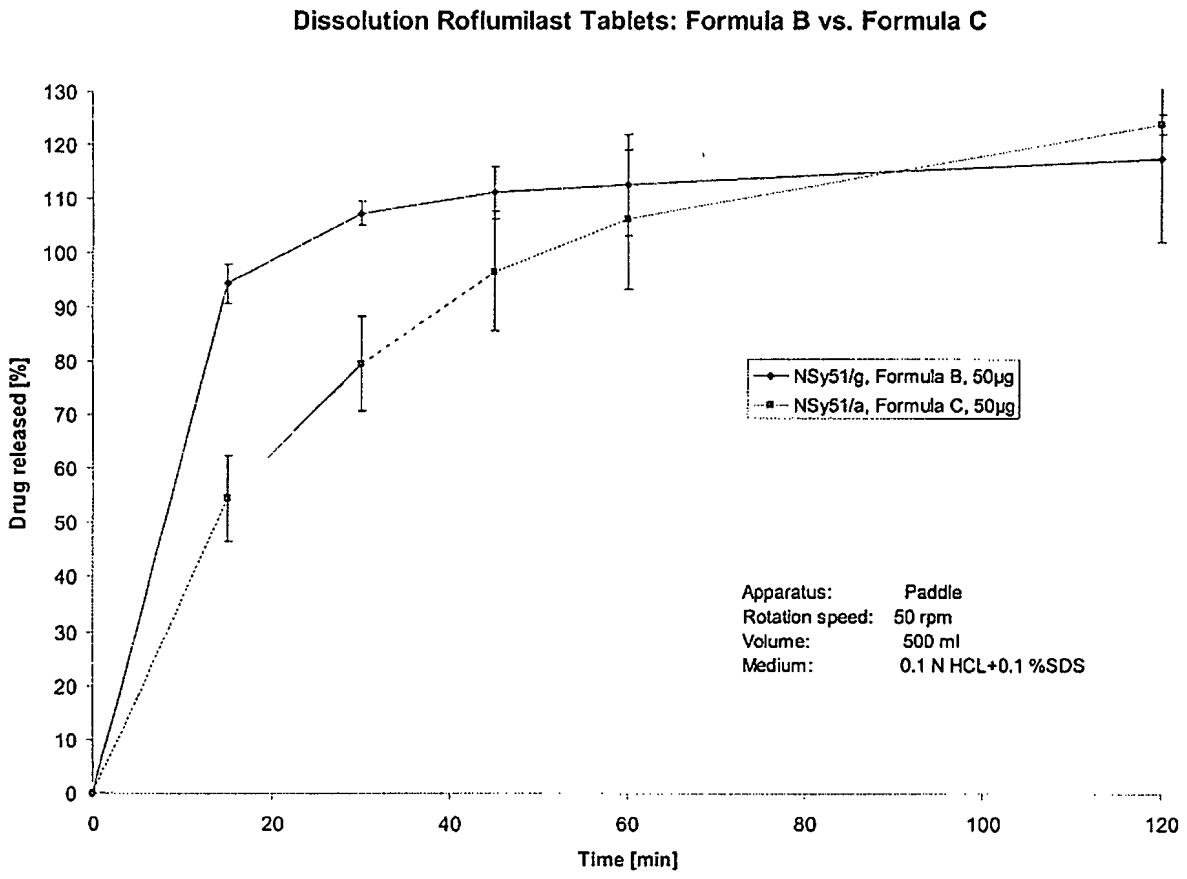


Figure 2

A comparison of Formulas B and C at the 50 µg roflumilast dosage amount clearly shows that Formula B, the formulation which contains PVP, has an unexpectedly higher dissolution rate of roflumilast than Formula C, which contains no PVP.

125 µg

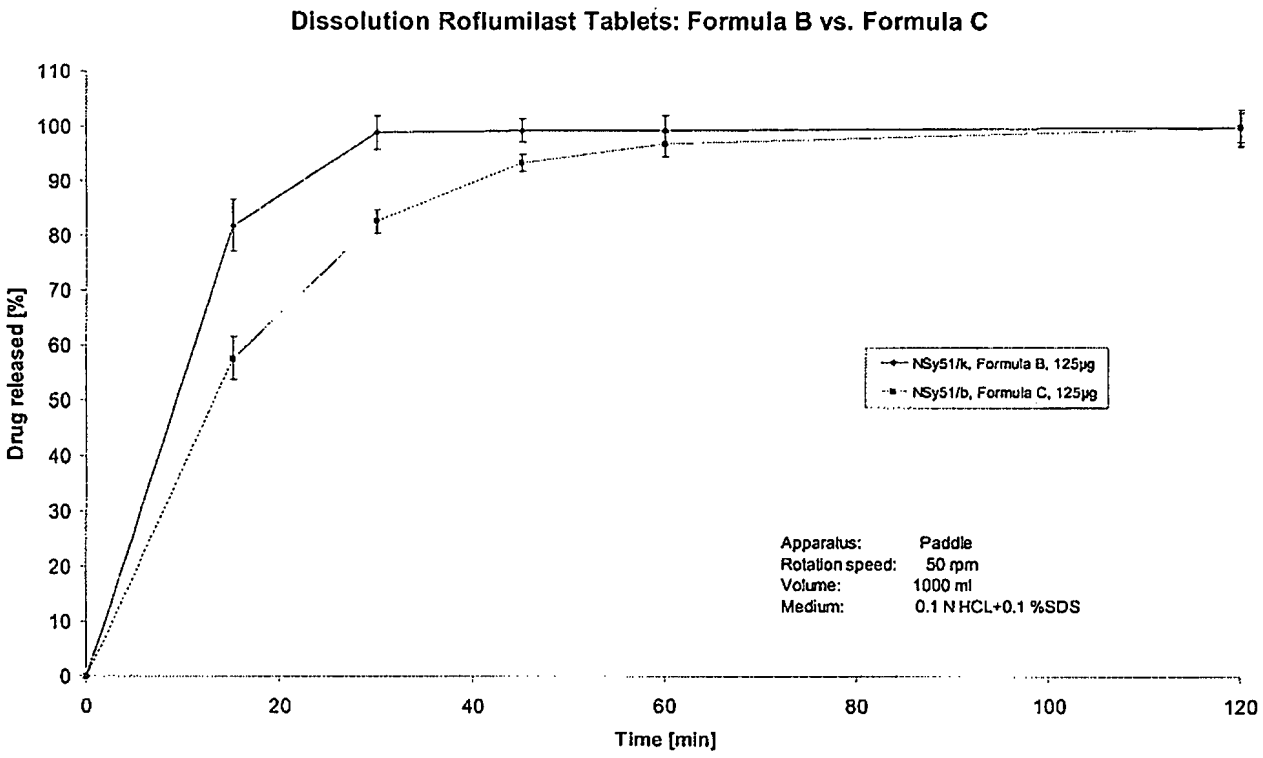


Figure 3

Similarly, a comparison of Formulas B and C at the 125 µg roflumilast dosage amount clearly shows that Formula B, the formulation which contains PVP, has an unexpectedly higher dissolution rate of roflumilast than Formula C, which contains no PVP.

250 µg

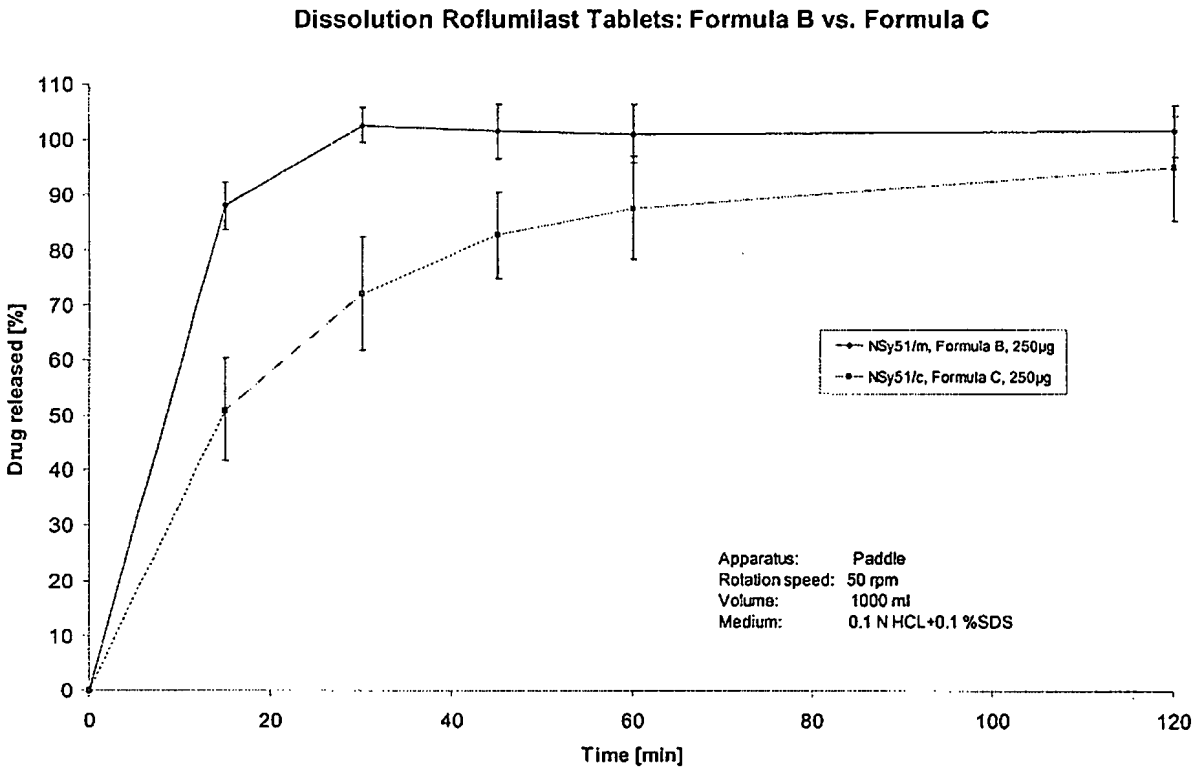


Figure 4

Similarly, a comparison of Formulas B and C at the 250 µg roflumilast dosage amount clearly shows that Formula B, the formulation which contains PVP, has an unexpectedly higher dissolution rate of roflumilast than Formula C, which contains no PVP.

500 µg

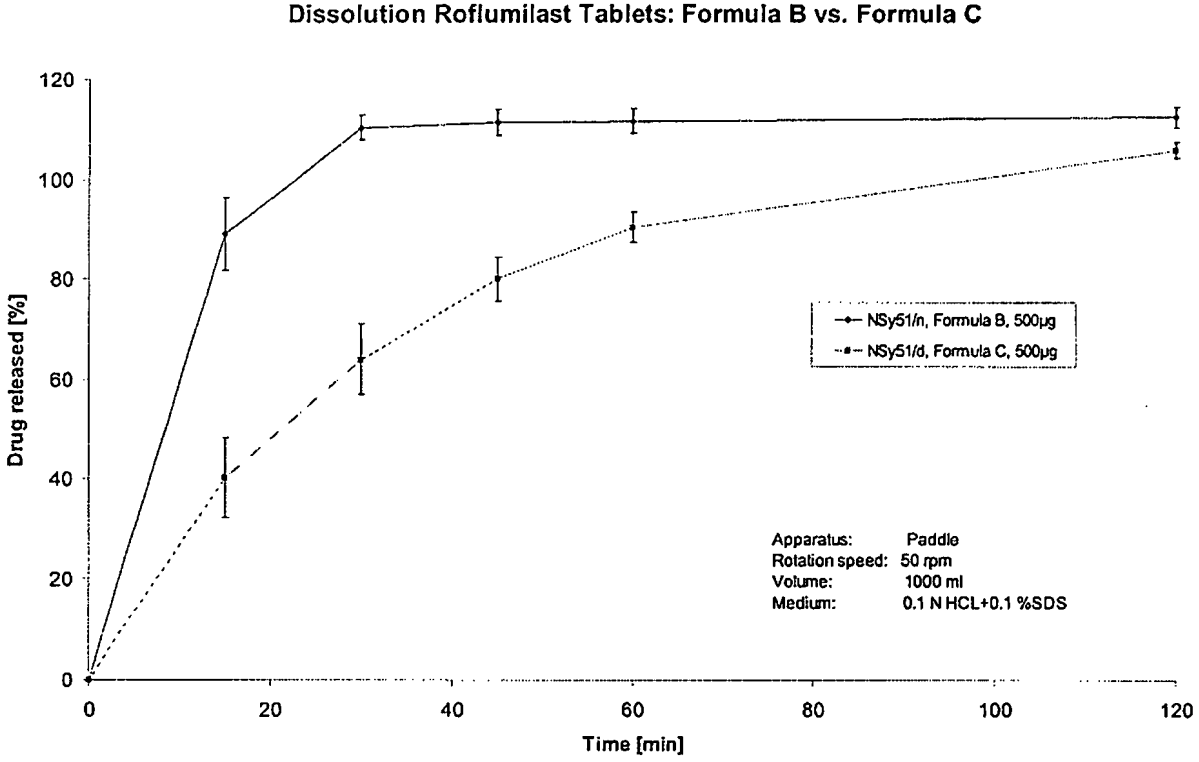


Figure 5

Similarly, a comparison of Formulas B and C at the 500 µg roflumilast dosage amount clearly shows that Formula B, the formulation which contains PVP, has an unexpectedly higher dissolution rate of roflumilast than Formula C, which contains no PVP.

1000 µg

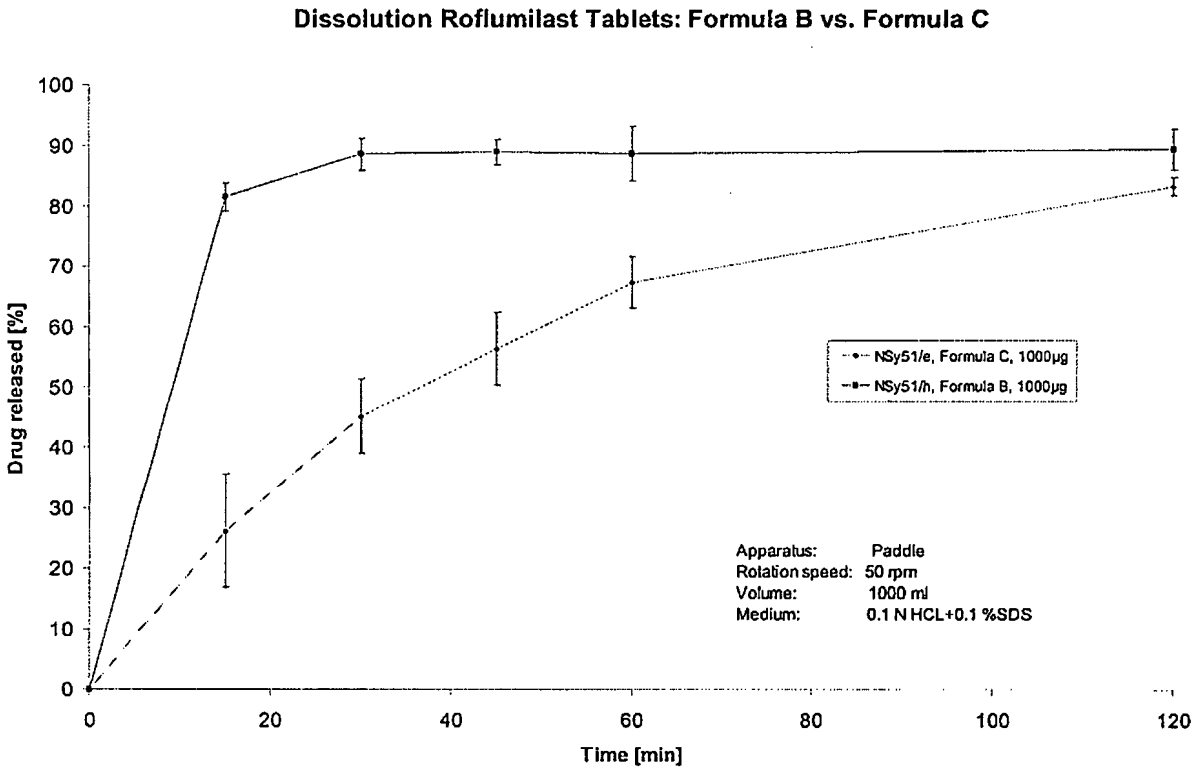


Figure 6

Similarly, a comparison of Formulas B and C at the 1000 µg roflumilast dosage amount clearly shows that Formula B, the formulation which contains PVP, has an unexpectedly higher dissolution rate of roflumilast than Formula C, which contains no PVP.

2500 µg

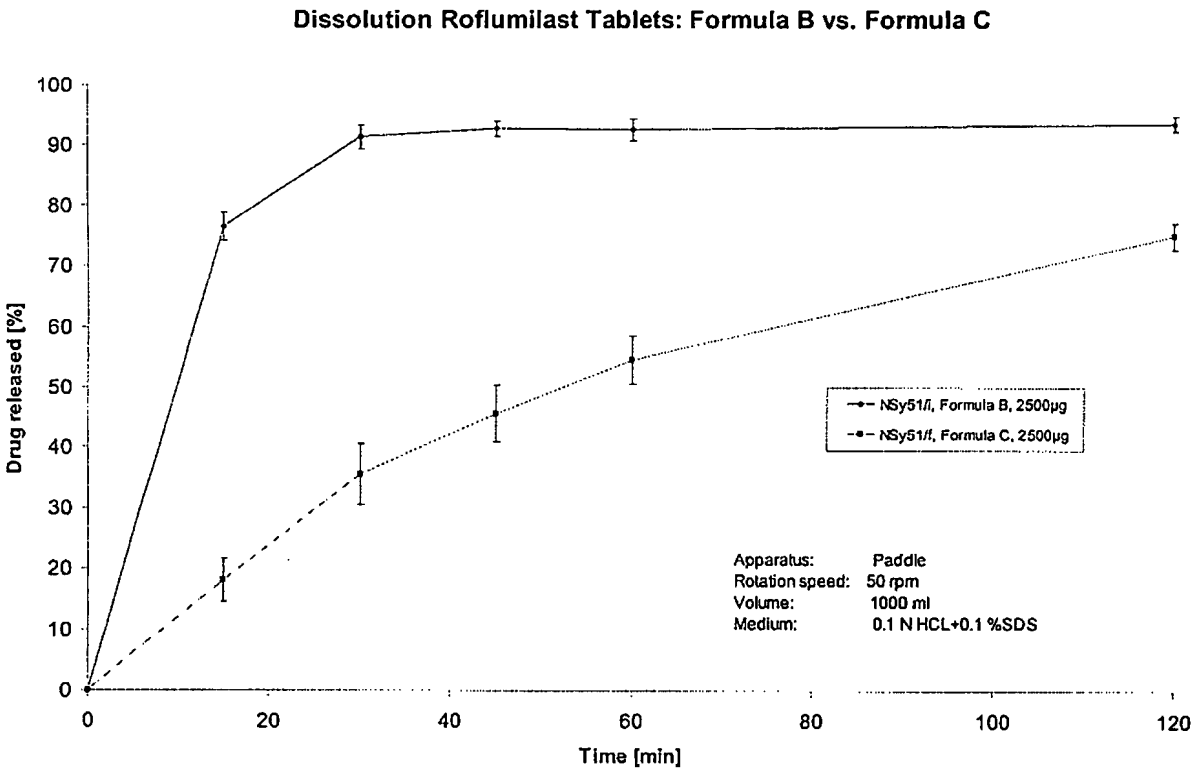


Figure 7

Similarly, a comparison of Formulas B and C at the 2500 µg roflumilast dosage amount clearly shows that Formula B, the formulation which contains PVP, has an unexpectedly higher dissolution rate of roflumilast than Formula C, which contains no PVP.